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DIPHTHERIA

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Diphtheria is an acute bacterial disease usually affecting the tonsils, pharynx, larynx, and nose caused by *Corynebacterium diphtheriae*. These organisms produce a toxin that is responsible for local tissue destruction and membrane formation.

In the 1980s and 1990s, diphtheria was nearly eliminated from industrialized countries. However there is a continuous risk of importation of toxigenic *C.diphtheriae* strains from endemic countries. In Sweden in the mid 1980s for example, after 20 years of absence of diphtheria, an outbreak of 80 cases resulted from importation. While only a handful of cases are reported each year in the U.S., serosurveys indicate that more than
40% of adults lack protective levels of circulating antitoxin.

Corynebacterium diphtheriae is an irregularly staining, Gram-positive, nonspore-forming, nonmotile, pleomorphic bacillus. Strains *of C. diphtheriae* may be toxicogenic or nontoxicogenic. The ability to produce toxin is mediated by bacteriophage infections of the bacterium and is not related to colony type.

Epidemiology

Because immunity to diphtheria wanes with time after immunization and because many adults either have not had a primary vaccination series or do not receive the recommended tetanus-diphtheria (Td) boosters every 10 years, half of U.S. adults are estimated to have levels of diphtheria antitoxin (antibodies to diphtheria toxin) below the level considered to be the lower limit of protection (0.01 International Units/ml).

Humans are the only known reservoir of C. diphtheriae.

Sources of infection include discharges from the nose, throat, eye, and skin lesions of infected persons. In addition, there are usually several infected carriers (persons infected with the C. diphtheriae bacteria in the nose and/or throat, but who do not have disease symptoms) who are contacts of the diphtheria case-patient. Carriers often augment the spread of the bacteria to other people.

Transmission results primarily from intimate contact with a patient or carrier; rarely, fomites and food-borne sources serve as vehicles of transmission.

Communicability in untreated persons usually lasts for 2 weeks or less, but occasionally persists for several months. In patients treated with appropriate antibiotics, communicability usually lasts less than 4 days. Occasionally, chronic carriage occurs, even after antimicrobial therapy.

Infection with *C. diphtheriae* can occur in the immunized individual. The ultimate aim is vaccination with diphtheria toxoid is the prevention of mortality by neutralization of circulating toxin through the production of antitoxin. Indeed, epidemiological studies of outbreaks have shown that immunization does

not prevent pharyngeal colonization with the organism but does reduce the incidence of and morbidity and mortality from diphtheria.

Children were more commonly affected before immunization became almost universal. In the vaccine era there has been a shift towards more adult cases. Illness is most common in groups living in crowded conditions.

The incubation period is usually 2 to 5 days but occasionally longer.

Clinical Description

In the respiratory form of the disease, a membrane is formed; this membrane is usually visible on the throat or tonsils. Respiratory diphtheria begins 2–5 days after infection with *C. diphtheriae*. Initial symptoms of illness include a sore throat and low-grade fever; swelling of the neck ("bullneck") from inflammation can develop and is a sign of severe disease. Persons may die from asphyxiation when the membrane obstructs breathing. Other complications of respiratory diphtheria are caused by remote effects of the diphtheria toxin, including myocarditis (inflammation of the heart) and nerve paralysis. The respiratory form of diphtheria usually lasts several days, and complications can persist for months.

Membranous pharyngitis from nontoxigenic *C. diphtheriae* is usually mild with no systemic complications; nontoxigenic *C. diphtheriae* may also cause bloodstream infections. Isolation of *C. diphtheriae* from the throat does not necessarily indicate a pathogenic role in the illness.
Although the frequency at which this occurs is unknown, a small percentage of the population may carry nontoxigenic or toxigenic strains of *C. diphtheriae* without disease symptoms.

Rarely, other *Corynebacterium* species (*C. ulcerans* or *C. pseudotuberculosis*) may produce diphtheria toxin and lead to classic respiratory diphtheria.

Other pathogens can cause a membrane of the throat and tonsils, including *Streptococcus* spp.; Epstein-Barr virus and cytomegalovirus, both of which cause infectious mononucleosis syndrome; *Candida*; and anaerobic organisms (Vincent's angina). The patient's health-care provider should be encouraged to perform appropriate laboratory tests to rule out these conditions.

Cutaneous diphtheria, caused by either toxigenic or nontoxigenic strains, is usually mild, typically consisting of nondistinctive sores or shallow ulcers and only rarely involving toxic complications (1% – 2% of infections with toxigenic strains).

Laboratory Tests

Specimens for culture should be obtained from the nose and throat and from any lesions. Material should be obtained from beneath the membrane, or a portion of the membrane itself should be submitted for culture. Because special media are required (Loeffler potassium tellurite agar) , the laboratory should be notified that *C. diphtheriae* is suspected. In remote areas, throat swabs can be placed in silica gel packs or telluride enrichment medium and sent to a reference laboratory for culture. When *C. diphtheriae* is recovered, the strain should be rested for toxicogenicity at the OPH laboratory.

All isolates of C. diphtheriae, from any body site (respiratory or cutaneous), whether toxigenic or nontoxigenic, should be sent to the CDC Diphtheria Laboratory for reference testing. Clinical specimens also should be sent to the CDC Diphtheria Laboratory for PCR testing. To arrange specimen shipping, contact OPH laboratory.

Biotype and toxigenicity testing: After *C. diphtheriae* has been isolated, the biotype (substrain) should be

determined. The four biotypes are intermedius, belfanti, mitis, and gravis. Also, toxigenicity testing using the Elek test should be performed to determine if the *C. diphtheriae* isolate produces toxin. These tests are not readily available in many clinical microbiology laboratories; isolates should be sent to a reference laboratory proficient in performing the tests.

CDC can perform a polymerase chain reaction (PCR) test on clinical specimens to confirm infection with a toxigenic strain. The PCR test can detect non-viable *C. diphtheriae* organisms from specimens taken after antibiotic therapy has been initiated. Contact your state health department to report a suspected case and to arrange laboratory testing.

Direct-stained smears and fluorescent antibody-stained smears are unreliable.

Serology

Measurement of the patient's serum antibodies to diphtheria toxin before administration of antitoxin may help in assessing the probability of the diagnosis of diphtheria. OPH laboratory can arrange to have testing done however delays in obtaining results would reduce their usefulness. If antibody levels are low, diphtheria cannot be ruled out, but if levels are high, *C. diphtheriae* is less likely to produce serious illness.

Surveillance

Diphtheria is a reportable condition with reporting required within 24 hours. Cutaneous diphtheria and respiratory disease caused by nontoxigenic *C. diphtheriae* should also be reported. All diphtheria isolates, regardless of association with disease, should be sent to the Office of Public Health laboratory for confirmation.

Case Definition

Clinical description

An upper respiratory tract illness characterized by sore throat, low-grade fever, and an adherent membrane of the tonsil(s), pharynx, and/or nose.

Laboratory criteria for diagnosis
- Isolation of *Corynebacterium diphtheriae* from a clinical specimen, or
- Histopathologic diagnosis of diphtheria

Case classification

Probable: a clinically compatible case that is not laboratory confirmed and is not epidemiologically linked to a laboratory-confirmed case.

Confirmed: a clinically compatible case that is either laboratory confirmed or epidemiologically linked to a laboratory-confirmed case.

Investigation

Prompt recognition and reporting of the disease is important to assure early, appropriate treatment with diphtheria antitoxin; to obtain necessary laboratory specimens before antibiotic or antitoxin treatment; to identify and evaluate contacts; and to provide necessary antimicrobial prophylaxis to prevent further spread. The outcome of the disease improves with early appropriate treatment.

▪ Upon receipt of a report of a suspected case of diphtheria preventive actions should start immediately without waiting for laboratory confirmation. Diagnosis is usually based on the clinical presentation since it is imperative to begin presumptive therapy quickly. Bacterial cultures will be completed by the hospital.
▪ Obtain the patient's history.

Information to collect
▪ Demographic information
- Name
- Address
- Date of birth
- Age
- Sex
- Ethnicity
- Race
- Country of birth
- Length of time in U.S.
▪ Reporting Source
- County
- Earliest date reported
▪ Clinical
- Hospitalizations: dates and duration of stay
- Date of illness onset
- Site of infection (e.g., nose, throat, larynx)
- Symptoms (e.g., fever, sore throat)
- Signs (e.g., neck edema, stridor, tachycardia)
- Complications (e.g., myocarditis, neuritis)
- Outcome (case survived or died)
▪ Date of death
▪ Postmortem examination results
▪ Death certificate diagnoses
▪ Treatment
- Date of administration of antitoxin
- Number of units of antitoxin given
- Antibiotics given
- Antibiotic dosage given
- Duration of therapy
▪ Laboratory
- Culture
- Biotype and toxigenicity test
- PCR
- Molecular typing
▪ Vaccine Information
- Dates and types of diphtheria vaccination
- Number of doses of diphtheria toxoid received
- Manufacturer name
- Vaccine lot number
- If not vaccinated, reason
▪ Epidemiological
- Contact with a probable or confirmed case
- Contact with immigrants or travelers to endemic areas
- Number of contacts cultured
- Results of contact cultures
- Travel history: 6 weeks prior to illness onset or date of presentation

Contact Investigation

- Identify contacts, trace sources of infection and define groups at special risk. Contacts consist of household members (usually limited to household members) and other persons with a history of habitual close contact with the person suspected of having the disease.
- Culture nasal or pharyngeal specimens from close contacts.
- Daily surveillance for 7 days for all close contacts in order to detect secondary cases.
- Immunize asymptomatic close contacts who are not fully immunized (defined as having had fewer than 3 doses of diphtheria toxoid) or whose immunization status is not known, using DTaP, DT, or dT, depending on age.
- Boost close contacts, especially household, with a diphtheria toxoid booster appropriate for age if they have not received a booster dose of diphtheria toxoid within five (5) years. Immunize children as appropriate for age.
- Antimicrobial prophylaxis
    - Oral erythromycin (40 to 50 mg/kg per day for 7 days, maximum 2 g/d)
    - or a single intramuscular injection of benzathine penicillin G (600 000 U for those weighing <30 kg and 1.2 million U for children weighing >30 kg and adults).
    - Contacts who cannot be kept under surveillance should receive benzathine penicillin G, but not erythromycin because adherence to an oral regimen is less likely, and a dose of DTaP, DT, or dT, depending on age and the person's immunization history.

The efficacy of antimicrobial prophylaxis is presumed but not proven. Repeated pharyngeal cultures should be obtained from contacts proven to be carriers at a minimum of 2 weeks after completion of therapy.

- Adult contacts whose occupations involve handling food, especially milk, or close association with unimmunized children (i.e., day care center employee) should be excluded from that work until bacteriological examination proves them not to be carriers.

Carrier immunization

- If not immunized, carriers should receive active immunization promptly, and measures should be taken to ensure completion of the immunization schedule.
- If a carrier has been immunized previously but has not received a booster within 1 year, a booster dose of a preparation containing diphtheria toxoid (DTaP, DT, or dT, depending on age) should be given.

Carrier antibiotic treatment

Carriers should be given antimicrobial therapy, specifically oral erythromycin or penicillin G for 7 days, or a single intramuscular dose of benzathine penicillin G (600 000 U for those weighing <30 kg and 1.2 million U for children weighing >30 kg and adults).

Follow-up cultures should be obtained at least 2 weeks after completion of therapy; if cultures are positive, an additional 10-day course of oral erythromycin should be given.

Erythromycin-resistant strains have been identified, but their epidemiologic significance has not been determined. Clindamycin, fluoroquinolones, rifampin, and newer macrolides, clarithromycin and azithromycin, have good in vitro activity and may be better tolerated than erythromycin, but they have not been critically evaluated in clinical infection or in carriers.

Immunization

Primary diphtheria immunization with diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP) is recommended for all persons at least 6 weeks old but less than 7 years of age and without a

history of contraindications. DTaP is the preferred vaccine for all doses in the vaccination series (including completion of the series in children who have received one or more doses of whole-cell DTP).

The primary vaccination with DTaP series consists of a three-dose series, administered at ages 2, 4, and 6 months, with a minimum interval of 4 weeks between the first three doses.

The fourth (first booster) dose is recommended at 15–18 months of age to maintain adequate immunity during preschool years. The fourth dose should be administered ≥ 6 months after the third. If the interval between the third and fourth doses is ≥ 6 months and the child is unlikely to return for a visit at the recommended age, the fourth dose of DTaP may be administered as early as age 12 months.

The fifth (second booster) dose is recommended for children aged 4–6 years to confer continued protection against disease during the early years of schooling. A fifth dose is not necessary if the fourth dose in the series is administered on or after the fourth birthday.

Routine tetanus booster immunization with Td, the adult formulation of tetanus and diphtheria toxoids, is recommended for all persons ≥ 7 years of age every 10 years. Because diphtheria disease does not always confer immunity, diphtheria toxoid vaccination should be undertaken during convalescence.

Health-care providers should ensure that travelers to all countries with endemic or epidemic diphtheria are up to date with diphtheria vaccination.

Case Management - Treatment

Antitoxin

Because the condition of patients with diphtheria may deteriorate rapidly, a single dose of equine antitoxin should be administered on the basis of clinical diagnosis, even before culture results are available. The site and size of the diphtheritic membrane, the degree of toxicity, and the duration of the illness are guides for estimating the dose of antitoxin. Suggested dose ranges are the following:

- pharyngeal or laryngeal disease of 48 hours' duration, 20,000 to 40,000 U;
- nasopharyngeal lesions, 40,000 to 60,000 U;
- extensive disease of 3 or more days duration or diffuse swelling of the neck, 80,000 to 120,000 U.
- Antitoxin is probably of no value for cutaneous disease, but some experts, nevertheless, recommend 20,000 to 40,000 U of antitoxin because toxic sequelae have been reported.

To neutralize toxin as rapidly as possible, the preferred route of administration is intravenous. Before intravenous administration, however, tests for sensitivity to horse serum should be performed with a 1:1000 dilution of antitoxin in saline. If the patient is sensitive to equine antitoxin, desensitization is necessary. Although intravenous immunoglobulins preparations contain antibodies to diphtheria toxin, their use for therapy of cutaneous or respiratory diphtheria has not been approved and optimal dosages have not been established.

Antitoxin can be obtained from the National Immunization Program of the Centers For Disease Control and Prevention.

Antimicrobial Therapy

Antimicrobial therapy consists of:

- Erythromycin given orally or parenterally (40 to 50 mg/kg per day, maximum 2 g /d) for 14 days;

- Penicillin G given parenterally (aqueous crystalline, 100 000 to 150 000 U/kg per day, in four divided doses intravenously; or aqueous procaine, 25 000 to 50,000 U/kg per day, maximum 1.2 million units, in two divided doses intramuscularly) for 14 days.

Antimicrobial therapy is required to eradicate the organism and prevent spread; it is not a substitute for antitoxin. Elimination of the organism should be documented by two consecutive negative cultures after completion of treatment.

Cutaneous Diphtheria. Thorough cleansing of the lesion with soap and water and administration of antimicrobials for 10 days are recommended.

Hospital precaution and isolation:

In addition to standard precautions, droplet precautions are recommended for patients and carriers with pharyngeal diphtheria until 2 cultures from both the nose and the throat are negative for *C. diphtheriae*. Contact precautions are recommended for patients with cutaneous diphtheria until 2 cultures of skin lesions are negative. Material for these cultures should be taken at least 24 hours apart after cessation of antimicrobial therapy.